

Objective identification of upper limb tremor in multiple sclerosis using a wrist-worn motion sensor: establishing validity and reliability

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Title: Objective identification of upper limb tremor in Multiple Sclerosis using a wrist worn motion sensor: establishing validity and reliability

Short Title: Objective tremor measurement in MS

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Abstract

Introduction

Over 25% of people with MS experience tremor, which may impact on activities of daily living and quality of life. Yet, there is no method to objectively measure tremor and effectiveness of interventions on tremor. This study aimed to test validity and reliability of a new objective measurement for upper-limb tremor in people with MS.

Methods

Twelve participants with MS who self-reported tremor were observed performing standardised tasks. Validity and reliability of a new method to detect tremor from wrist movement was established against Occupational Therapist observation of tremor (FAHN). Concurrent validity of severity (displacement) of tremor was assessed. Responsiveness to change in tremor characteristics was explored in a sub-set of participants using weighted wrist-cuffs.

Results

The new method correctly predicted 98.2% of tremor cases identified by the Occupational Therapist with high sensitivity (0.988) and specificity (0.976). Calculated displacement of tremor correlated with FAHN tremor severity scores moderately ($r_s=.452, p=.004$). The

new measure was responsive to changes in tremor characteristics due to change in weight of wrist-cuffs.

Conclusion

The new method of characterising tremor in those with MS demonstrated excellent validity and reliability in relation to Occupational Therapist's identified tremor, and could provide valuable objective insight into efficacy of interventions.

Keywords (max 6)

Multiple Sclerosis, Tremor, Upper limb, Measurement, Accelerometry, Intervention

Introduction

Multiple Sclerosis (MS) is one of the most prevalent inflammatory diseases of the central nervous system in young adults (Compston & Coles, 2008). The neurodegenerative process of this autoimmune disease attacks white matter and causes damage in different regions of the brain leading to a variety of symptoms, such as fatigue, sensory problems, pain, visual problems, mobility and balance issues, dysfunction of the bowel and urinary tracts and tremor.

Between 25 and 58% of people with MS reportedly experience tremor (Alusi, Worthington, Glickman, & Bain, 2001; Pittock, McClelland, Mayr, Rodriguez, & Matsumoto, 2004; Rinker et al., 2015). Tremor is described as an involuntary rhythmic movement of one or several body parts/limbs which results from contraction and relaxation of muscle groups (Deuschl, Bain, & Brin, 1998). The upper limbs were found to be the most frequently affected body part in people with MS, with tremor usually being associated with maintenance of particular postures (postural) or associated with the performance of activities (intention) (Alusi et al., 2001; Pittock et al., 2004). Tremor affecting the upper limb can affect the ability to control voluntary movement and lead to difficulties in performing functional everyday tasks such as eating, drinking and self-care. Therefore tremor is of considerable concern to people with MS and to Occupational Therapists that have a key role in supporting engagement and participation in meaningful and purposeful occupations.

Tremor is most commonly assessed clinically, using rating scales that are based on a clinician's visual observation and self-report (e.g. FAHN; (Fahn, Tolosa, & Marin, 1988)). While these have been shown to be a valid and reliable assessment for tremor in MS (Hooper, Taylor, Pentland, & Whittle, 1998) they do require the presence of a trained clinician at all times. It has also been demonstrated that outcomes may differ between examiners. Furthermore, tremor occurrence may vary over time meaning that one off observation may be insufficient to characterise tremor occurrence. An objective method of measuring tremor with a conveniently wearable motion sensor would eliminate the need for subjective visual observation and allow long term tremor monitoring.

It has been demonstrated that it is possible to objectively measure tremor using body worn monitors (Breit, Spieker, Schulz, & Gasser, 2008; Heldman et al., 2011; Ketteringham, Neild, Hyde, Jones, & Davies Smith, 2011). However, these studies have

mainly concentrated on people with severe tremor in Parkinson's or Essential tremor. It has also been shown that objective measurement techniques can measure a change in tremor that is not reflected in clinical tremor severity scales (Hewer, Cooper, & Morgan, 1972; Morgan, Hewer, & Cooper, 1975). However, this work on mixed populations has failed to fully acknowledge that tremor in MS has different characteristics to that in other conditions. It has been suggested that tremor in MS occurs at lower frequencies of movement (Deuschl et al., 1998) and therefore its detection will require different methods of analysis. Evidence providing a robust description of tremor characteristics in those with MS is limited. Also, automatic identification of tremor in MS has not been reported.

The objective characterisation of tremor in people with MS is necessary to provide quantitative information on current symptoms and allow the efficacy of interventions to be investigated effectively. Such a method could strengthen the evidence underpinning interventions aimed at reducing tremor.

Within the current study it was hypothesised that the output from a wrist worn monitor (accelerometer) could be used to automatically identify and characterise upper limb tremor in people with MS. To establish the validity of the developed method the test accuracy had to be established against the current gold standard. Furthermore it was hypothesised that the developed method would be sensitive to changes in tremor characteristics associated with an intervention (weighted wrist-cuffs).

Methods

Participant recruitment

Ethical approval was gained from the West of Scotland Research Ethics Committee (13-WS-0253) for recruitment within the UK National Health Service and the Glasgow Caledonian University Ethics Committee for recruitment outside of the NHS. All participants gave written informed consent. Participants were recruited through clinics in Greater Glasgow and Ayrshire (identified by clinical staff) as well as online through the MS Society and through community centres (self-identification). For inclusion, participants had to be above 18 years old, had to have a definite diagnosis of MS according to the McDonald criteria (Polman et al., 2011), and clinically identified or self-report tremor in one or both upper limbs. Potential participants were excluded if they had a history of tremor before the diagnosis of MS, if they experienced any other neurological conditions apart from MS or if they had experienced a relapse within the last 30 days.

Data collection

Upper limb movement was objectively measured using a wrist worn movement monitor. This consisted of a triaxial accelerometer (9gram) (AX3 –Axivity, Newcastle, UK) attached to the wrist of each participant's most affected arm. The motion sensor was mounted in a plastic casing (13gram) and fixed to the arm using hydrogel pads (PAL Stickies, PAL Technologies Ltd, Glasgow, UK). It was positioned dorsally on the forearm approximately 4cm proximal to the wrist. Data samples were recorded 100 time per second (100Hz) with a range of up to ± 8 time acceleration due to gravity (g_0 = gravitational constant = 9.81ms^{-2}). The sensitive axes of the sensor were aligned with the long axis of the forearm, at right angles to the dorsal surface of the wrist and with the third axis perpendicular to these two.

The identification of occurrences of tremor was achieved using the current clinical gold standard, a modified Fahn-Tolosa-Marin tremor rating scale (FAHN) (Fahn et al., 1988), during a number of tasks, described below. Tremor occurrence was identified by an HCPC registered Occupational Therapist, with over 30 years of experience with tremor in MS. The FAHN tremor severity scores are based on the movement amplitude, with more severe tremor being linked to larger displacement due to tremor. The 5-point-scale was used, defined as follows:

- 0 – no tremor
- 1 – mild tremor (<1cm, may be intermittent)
- 2 – moderate tremor (1-5cm, may be intermittent)
- 3 – marked tremor (5-10cm)
- 4 – severe tremor (>10cm)

Participants were asked to perform a number of standardised activities taken from the FAHN tremor rating scale and the Action Research Arm Test (ARAT) (Lyle, 1981) as a set of standardised tasks for an initial tremor assessment. All ARAT tasks were targeted movements that might allow the observation of intention tremor. All tasks, bar one, were unilateral and participants were allowed to practise each task with the “non-measurement” arm before each task was performed with the measurement arm for analysis purposes. The following tasks were performed by participants:

- Task 1 (FAHN): Maintaining posture against gravity - both arms outstretched in front of the body, shoulders in 90° flexion.

- Task2 (FAHN): Movement against gravity - arm stretched vertically to the lateral side, shoulder in 90° abduction, then the finger was brought to the nose three times by flexing the elbow.
- Task 3 (FAHN): Pouring water - from one firm plastic cup (8cm tall, 7cm in diameter) to another, not resting them on each other.
- Task 4 (ARAT): Pick up a wooden cube, edge length 10cm, and place it on the shelf of the ARAT table (37cm above the table surface).
- Task 5 (ARAT): Repeat task 3.
- Task 6 (ARAT): Move two hollow metal tubes (diameter 2.5 and 1cm) and place them over stick-holders at the back of the table (30cm to the back, 5cm raised from the table top).
- Task 7 (ARAT): Pick up a ball bearing (diameter of 6mm) between the thumb and ring finger and place it in a petri dish on the shelf of the ARAT table.
- Task 8 (ARAT): Bring the hand from a resting position on the thigh to the back of the head.
- Task 9: Self-selected daily activity affected by tremor.

To assess the responsiveness of the new method of tremor detection weighted wrist-cuffs were used. A custom made wrist-cuff was attached with two straps, distally and proximally to the monitor, with weights on the anterior aspect of the forearm. Participants were asked to complete Task 4 for three sets of five repetitions. One set each was performed with no weight (weight 0), 500g (weight 1) or 1000g (weight 2). The choice of the weights was based on previous studies (Hewer et al., 1972; Morgan et al., 1975). The order of the weights 1 and 2 was randomized to attempt to reduce the influence of fatigue on the outcomes.

Data analysis

The new method of identifying tremor used the acceleration signal generated by the wrist worn monitor. This was accomplished by investigating short time windows of 2s each. To increase the temporal resolution the window was only moved by one second, resulting in overlapping windows. Fast Fourier Transforms (frequency analysis) were used to identify the frequency components in all three dimensions of the movement. Tremor for those with MS has previously been reported in the range of 3-8Hz, i.e. oscillations in motion occur between 3 and 8 times per second (Alusi et al., 2001; Pittock et al., 2004). However, these previous reports of tremor are limited. Therefore the current algorithm

isolated all movements occurring from 3-15Hz to ensure all possible tremor was detected, yet eliminating the detection of high frequency noise within the signal. Using a lower limit of 3Hz prevented the interpretation of usual movements as tremor. If movements within the 3-15Hz range were detected in two of the three dimensions then a true tremor event was considered to have occurred. A minimum magnitude of tremor was also set, effectively defining detected tremor having a magnitude greater than 0.27cm (an acceleration value of 0.05 g₀). Where tremor was detected the frequency of movement and the maximum displacement were calculated (assuming a smooth sinusoidal tremor movement) (Davies & Crann, 2004). The maximum displacement was defined as the peak to peak movement due to tremor.

As the FAHN tremor severity scores are based on the movement magnitude it was possible to directly compare the displacement calculated from the new method with that observed and classified using the FAHN.

All tremor occurrences identified using the new method (index test) were compared against the reference standard of clinically assessing tremor (the target condition) with the use of the FAHN tremor rating scale according to the guidelines of the Cochrane Handbook (Davenport, Takwoingi, Leeflang, & Deeks, 2014) to establish its accuracy. Sensitivity and specificity of the index test were assessed using ROC curves comparing the new method against the gold standard of clinically assessing tremor. Also, to investigate concurrent validity the correlation between the therapist's tremor rating and the calculated displacement was assessed using Spearman's correlation coefficient. Only tremor occurrences as identified by the therapist were used for calculating the correlation. All statistical analysis was performed using SPSS (Version 22, IBM, USA) with $p < 0.05$ for significance. The strength of the correlation coefficient was interpreted according to Cunningham, Weathington, & Pittenger (2013).

To assess if the new method was responsive to differences in tremor characteristics induced by the weighted wrist-cuffs, differences in frequency and displacement were calculated between the baseline condition (weight 0) and weights 1 and 2.

Results

Twelve adults (7 female/5 male, mean age: 51.5 ± 14.1 years) with MS (disease duration 13.9 ± 9.1 years) were recruited. Tremor was self-reported in all 12 participants. Seven participants were diagnosed with relapsing remitting and 5 with secondary

progressive MS. Expanded Disability Status Scores (EDSS) were not available for most participants and therefore not reported. Using the FAHN criteria, tremor was observed and identified at the wrist in only five participants during the standardised activities. Of these 5, 4 performed tasks using the weighted wrist-cuffs (one participant declined to take part due to fatigue). The average FAHN scores for the five participants experiencing tremor were 2.4 (± 0.5) for P003, 3.0 (± 0.9) for P007, 1.1 (± 0.3) for P009 and 1.0 (± 0.0) for P010 and P011.

One hundred and sixty eight activities (12 participants x 9 standardised activities plus 4 participants x 15 repetitions weight 0/1/2) were observed and rated for tremor using the FAHN tremor severity rating scale. The developed algorithm (index test) showed high sensitivity (0.988), high specificity (0.976) and high accuracy by correctly predicting 82 (98.2%) tremor cases, identified by the therapist through observation (Table 1). Only one false negative and two false positives occurred across all 168 cases. When looking only at participants who exhibited tremor in the assessments (106 cases), the sensitivity stayed the same but with a higher specificity (1.0) as no false positives occurred in those with tremor.

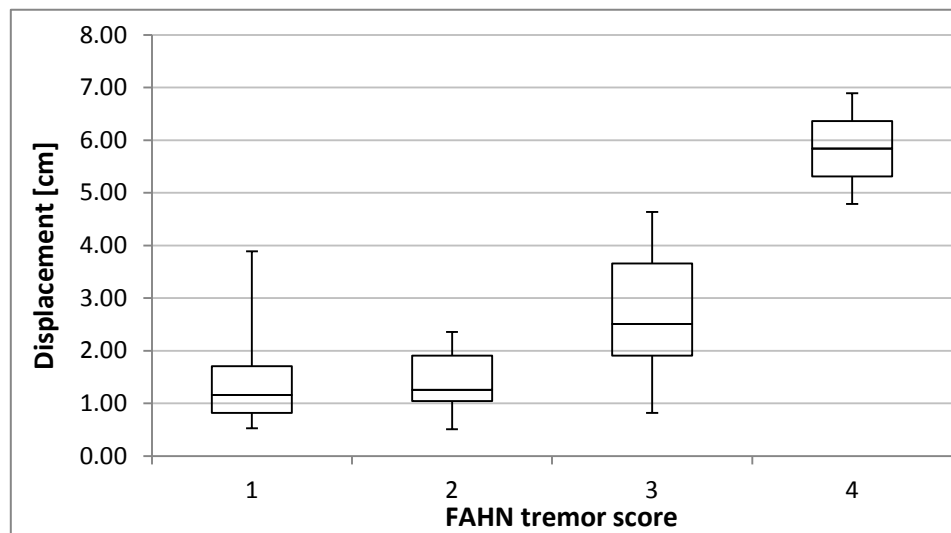
Table 1: A comparison of the outcomes of the tremor identification by the therapist (reference standard) and the algorithm (index test). For each outcome two results are given. The first is for all tasks and all participants; the second is for only those who exhibited tremor. The number of occurrences and percentage within each category is given.

		Therapist identified (reference standard)			
		Positive		Negative	
		All participants	Only those exhibiting tremor	All participants	Only those exhibiting tremor
Algorithm identified (Index test)	Positive	82 97.6%	82 97.6%	1 1.2%	0 0%
	Negative	2 2.4%	2 2.4%	83 98.8%	22 100%

From all observations of the standardised tasks of the initial tremor assessment (12 participants x 9 standardised activities) tremor occurred in only 38 instances with a mean frequency of $5.5 \pm 2.7\text{Hz}$ (range 3.9 to 13.0Hz). One participant (P003) in particular experienced tremor of very high frequency during all these tasks (mean = $11.2 \pm 1.3\text{Hz}$). Calculated displacement at the wrist was between 0.75 to 6.89cm.

Concurrent validity of the magnitude of tremor calculated using the new method and that of the Occupational Therapist's rating using the FAHN tremor severity scores indicated a moderate positive and significant correlation (Spearman's correlation coefficient = .452, $p = .004$). However, while the displacement of tremor calculated using the new method was quite distinct between FAHN severity scores of 2, 3 and 4, those for the scores of 1 and 2 were nearly identical with displacement medians of 1.16 and 1.26cm respectively (Figure 1). Also, the calculated tremor displacement did not align with the definition of the FAHN severity scores as rated by the Occupational Therapist. Only one third of all 'mild'-tremors were <1cm with the median also being above this upper boundary. Moderate (2) tremors were all measured at the lower end of the defined spectrum. Marked (3) and severe (4) tremors were both measured below the defined lower amplitude boundary with medians of 2.5cm and 5.8cm.

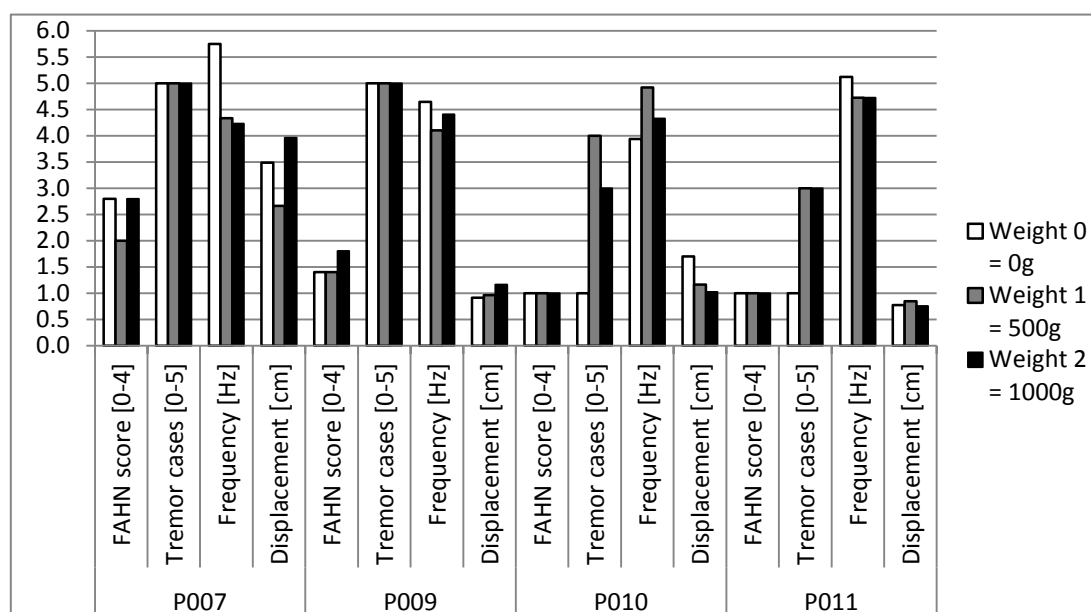
Figure 1: Displacement due to tremor calculated using the new method by FAHN rating (1/mild - 4/severe). All episodes of tremor within each FAHN score from all participants are included. Box plots including median, interquartile ranges and minimum and maximum values.



The average FAHN tremor severity score (0-4) and the number of tremor cases occurring during the repetitions of the weighted tasks are illustrated in Figure 2. While the FAHN tremor score did not change in participants P010 and P011, the number of tremor

occurrences increased when using the weighted wrist-cuffs. Following the application of the weighted wrist-cuff, the maximum tremor frequency averaged over all tremor occurrences decreased in all but one participant (P010). The outcomes for displacement were not coherent across the participants and over the three conditions.

Figure 2: Mean FAHN score (0-4), the number of tremor cases (0-5), mean objectively measured tremor frequency [Hz] and displacement [cm] under the three weight conditions. Each value is the mean of tremor detected within the 5 repetitions.



Discussion

A new objective measurement method was developed to measure upper limb tremor in MS, based on a wrist worn movement sensor. The method proved to be valid, demonstrating high specificity and sensitivity against the current gold standard of therapist tremor identification. Furthermore, the measure was responsive to change induced by an intervention.

The comparison of the outcomes of the new objective method with the current gold standard of clinical tremor identification (i.e. the FAHN, Table 1) showed that the new

method was able to identify tremor accurately with high specificity and sensitivity. The index test detected only two incidences of tremor where none was observed. In one case the participant voluntarily shook their hand in a tremor like movement. Clinically this was not classified as tremor, due to the voluntary nature of the action, yet the new method classified it as tremor. The second false positive was less clear as no rhythmic or tremor like movement was observable. This instance occurred when a participant quickly pulled back their arm after fitting the hollow tube over the fitted holder to pick up the second tube in Task 6. In the one case that the new method was not able to identify an observed tremor, the Occupational Therapist indicated that this was a borderline case. It occurred during a personal choice activity when a participant simulated the use of an electric shaver. While the movement was certainly affected by the interference of a movement disorder, it was unclear if it was tremor as the arm jerked, but not in a rhythmic movement. Nonetheless, the Occupational Therapist decided to rate this as tremor. However, the overall accuracy of the new method, to correctly classify 98% of cases as tremor or non-tremor, indicates a high level of validity within this population of people with MS.

Identified tremor movements mostly occurred within the frequency range of 3-8Hz that was previously reported (Alusi et al., 2001; Labiano-Fontcuberta & Benito-León, 2012; Pittock et al., 2004). However, one participant in particular experienced a very high frequency tremor, with an average peak frequency of 11.2Hz, during the initial tremor assessment. This was above the 8Hz upper limit for MS related tremor previously reported, suggesting that tremor frequencies outside this range can occur. However, it is possible that this high frequency tremor originated from co-morbidities. While having any other neurological condition or movement disorder(s) were exclusion criteria, and the medical record of these participants did not indicate either, no formal neurological screening was carried out prior to participation in this study.

For tremor, as characterised by the new method, to be related to tremor severity, as assessed clinically using the FAHN, it was important that there was a clear relationship between the two outcome measures. The concurrent validity between the clinically observed tremor amplitude (as characterised by the FAHN rating) and that derived from the new method, indicated a moderate positive and significant correlation. However, the agreement of severity scores, and their definition, and the calculated displacement was not consistent across the range of tremor severities. Between categorisations at the lower end of the FAHN scale (mild to moderate, values 1-2) the objective measurements demonstrated little difference in actual tremor displacement and were lower than FAHN definitions (Figure 1). At the upper end of the FAHN scale (moderate, marked, severe,

values 2-4) the objective measurement did demonstrate differences in displacement, but these were still lower than those observed based on the FAHN scale. This indicates that the Occupational Therapist may have overestimated the displacement of tremors with peak to peak amplitudes larger than 2.5cm. The motion sensor used in this study was attached at the wrist and so only recorded a signal at that point on the arm. It is possible that an observer uses a more global understanding of the movement, perhaps giving a higher rating where the whole arm or hand movements appeared to have high displacement magnitude. Also, the calculation used in the new method treated each axis of movement independently, using only the axis of movement with the highest frequency to calculate the displacement due to tremor. This may have underestimated the true displacement if the tremor movement was not aligned with this axis of the motion sensor. This underestimate of the true three-dimensional tremor displacement magnitude may explain part of the difference compared to the therapist observed FAHN ratings. To overcome this short coming an absolute measure of displacement would have been required. This would have required additional instrumentation to allow calculation of full three-dimensional motion of the wrist.

This study demonstrated that the new objective method to measure tremor is sensitive to changes in tremor characteristics following the application of a weighted wrist-cuff. There is, therefore, the potential to use this method within a clinical setting to objectively explore the efficacy of interventions on tremor. The potential benefit of using an objective tremor measure was reinforced by the therapist's observation that the gold standard clinical tremor severity scoring was not sensitive enough. Figure 2 shows that especially in the case of P010 the therapist felt that tremor severity decreased with the use of the weights, however, this change could not be reflected in the scoring. The FAHN scores indicated change in tremor severity in two participants. In P007 a lower severity was scored for weight 1 than for no weight. In P009 tremor was scored equally for conditions 0 and 1 but higher for weight 2. The outcomes showed the newly developed method was able to identify changes in tremor characteristics when using the weighted wrist-cuff which the tremor unaffected or increased with the application of weights. In P007 the light weight was able to reduce tremor amplitude, but the heavier weight increased tremor amplitude. This may suggest that weights need to be individually chosen to the needs of patients. Overall, there was no trend in outcomes indicating that weights could be used to consistently alleviate the symptoms of tremor either through frequency or displacement reduction. A study on a larger population may be able to provide more insight in regards to the effectiveness of weighted wrist cuffs as an intervention.

Finally, it has to be mentioned that the objective tremor measurement methods was readily accepted by all participants. In this study, a rudimentary attachment method was used that combined a plastic casing and sticky tape. However, through advances in the development for this particular sensor, it is now possible to wear the sensor in a lightweight rubber wrist band that resembles a small watch. This does not only increase patient comfort, but also reduced the weight from 22 to 16gram. An early study in the field of tremor has shown that the weight of measurement tools itself can affect tremor (Stiles & Randall, 1967), with the latest devices this is becoming less of an issue for routine measurement.

The new method demonstrated high levels of validity and reliability for the detection of tremor in comparison to the current gold standard within the sample studied. However, a larger study is required to demonstrate the generalizability of this method in the wider MS population. Whilst this study recruited those with MS who were identified by clinicians or self-reported tremor it was not possible to observe the occurrence of tremor in a proportion of the participants. This suggests that tremor occurrence may be intermittent in those with MS. One form of MS is relapsing remitting which may explain the lack of observable tremor in some participants even when performing activity that they self-selected as being affected by tremor. This finding suggests that future studies of tremor in MS may have to perform tremor assessment on several occasions to ensure tremor occurrence is observed.

Conclusion and Implications for clinical practice

This study has demonstrated that automatic objective identification, and characterisation of upper limb tremor in people with MS is possible using a wrist-worn movement sensor (accelerometer) using a bespoke signal interpretation based on examining the frequency of movement. Over 98% of tremor occurrences, as identified by an experienced Occupational Therapist, were correctly identified by the new method.

Tremor in MS was identified within this sample of people with MS with a frequency of tremulous movement between 3.5 and 13.0Hz and a movement displacement of 0.75 to 6.89cm. This showed that tremors of higher frequencies than previously reported might occur in those with MS. This possibility should not be excluded in clinical practice and future research on MS tremor.

The new method was responsive to changes in the displacement and frequency of tremor following an intervention (weighted wrist-cuffs) that were not always highlighted by changes in clinical ratings using the FAHN scale. Therefore the new method offers the opportunity to implement a more sensitive means of tremor characterisation, whilst removing subjectivity of the observer from the assessment. This might be essential to find interventions that are helpful to patients.

The current implementation of this method uses custom written software for data analysis. To make this analysis available more widely and allow routine clinical use the algorithm would have to be integrated into a device and a user-friendly interface developed.

Objective characterisation of tremor in people with MS appears to be feasible and offers the opportunity to explore the efficacy of interventions aimed at reducing tremor.

Key messages

Key findings

- 1) Movement at the wrist can be used to identify upper-limb tremor in MS.
- 2) Objective measurement of tremor severity is correlated with, but not identical to, occupational therapist's subjective assessment.

What the study has added

A new method of objectively measuring upper-limb tremor in MS with high levels of validity and reliability is demonstrated, offering the opportunity to assess efficacy of interventions for tremor reduction.

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Research ethics

Ethical approval was gained from the West of Scotland Research Ethics Committee (13–WS-0253) for recruitment within the UK National Health Service and the School of Health and Life Sciences' Ethics Committee of Glasgow Caledonian University for recruitment out-with the NHS. All participants provided written informed consent

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

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